

PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

To:

United States Patent and Trademark
Office
(Box PCT)
Washington D.C. 20231
United States of America

in its capacity as elected Office

Date of mailing: 26 May 1995 (26.05.95)	
International application No.: PCT/US94/10945	Applicant's or agent's file reference: ARCD146P--
International filing date: 27 September 1994 (27.09.94)	Priority date: 27 September 1993 (27.09.93)
Applicant: DRMANAC, Radoje	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

25 April 1995 (25.04.95)

in a notice effecting later election filed with the International Bureau on:

2. The election was
 was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer: B. Schmitt Telephone No.: (41-22) 730.91.11
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PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Washington D.C. 20231
United States of America

Date of mailing (day/month/year)

13 November 1995 (13.11.95)

in its capacity as elected Office

International application No.

PCT/US94/10945

International filing date (day/month/year)

27 September 1994 (27.09.94)

Applicant

ARCH DEVELOPMENT CORP. et al

The International Bureau transmits herewith the following documents and number thereof:

copy of the international preliminary examination report and annexes (Article 36(3)(a))

The International Bureau of WIPO
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1211 Geneva 20, Switzerland

Authorized officer

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A21911PC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/ US 94/ 10945	International filing date (day/month/year) 27/09/1994	Priority date (day/month/year) 27/09/1993
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant ARCH DEVELOPMENT CORP. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

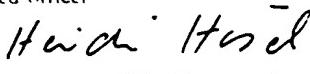
2. This REPORT consists of a total of 7 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of 15 sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 25/04/1995	Date of completion of this report 08. 11. 95
Name and mailing address of the IPEA;  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  H. Hoesel Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/12305

directed only to a pool of probes which may have many other uses and also contain limitations therein to specific positions in probes in the pool which are not recited in Group II. Thus, Groups II and III lack unity of invention in not containing the same special technical feature for probes in a pool or pools therein. Groups IV-VII all are directed to arrays similar to that cited in Group I but are directed to completely different specific reference genes. Therefore Groups IV-VII lack unity of invention with Groups II and III for the same reasons as discussed above regarding Group I. Additionally the completely different and totally unrelated specific references genes cited in Groups IV-VII therefore are directed to a different specific reference gene which is deemed the special technical feature of these Groups when each of Groups I and IV-VII are compared to any other Group therein. In summary the claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.

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The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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CLAIMS

1. A method for determining the sequence of a nucleic acid molecule, comprising the steps of:

- (a) identifying sequences from the molecule by hybridizing the molecule to complementary sequences from two sets of small oligonucleotide probes of known sequence, wherein the first set of probes are attached to a solid support and the second set of probes are labelled probes in solution;
- (b) identifying overlapping stretches of sequence from the sequences identified in step (a); and
- (c) assembling the nucleic acid sequence of the molecule from said overlapping sequences identified.

2. The method of claim 1, wherein said hybridization is carried out in cycles.

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3. A method for determining the sequence of a nucleic acid molecule, comprising the steps of:

- (a) fragmenting the nucleic acid molecule to be sequenced to provide intermediate length nucleic acid fragments;
- (b) identifying sequences from said fragments by hybridizing the fragments to complementary sequences from two sets of small oligonucleotide probes of known sequence, wherein the first set of probes are attached to

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a solid support and the second set of probes
are labelled probes in solution;

5 (c) identifying overlapping stretches of sequence
from said sequences identified in step (b); and

(d) assembling the nucleic acid sequence of the
molecule from said overlapping sequences
identified.

10

4. The method of claim 3, wherein said fragments are
sequentially hybridized to complementary sequences from
two sets of small oligonucleotide probes of known
15 sequence.

20 5. The method of claim 3, wherein said fragments are
simultaneously hybridized to complementary sequences from
two sets of small oligonucleotide probes of known
sequence.

25 6. The method of claim 3, wherein said intermediate
length nucleic acid fragments are between about
10 nucleotides and about 40 nucleotides in length and
said small oligonucleotide probes are between about
4 nucleotides and about 9 nucleotides in length.

30

7. The method of claim 3, wherein said oligonucleotide
probes hybridize to completely complementary sequences
from said fragments.

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8. The method of claim 3, wherein said oligonucleotide probes hybridize to immediately adjacent sequences from said fragments.

5 9. The method of claim 8, wherein said oligonucleotide probes hybridize to completely complementary and immediately adjacent sequences from said fragments.

10 10. The method of claim 8, wherein said immediately adjacent oligonucleotide probes are subsequently ligated.

15 11. The method of claim 3, wherein step (b) comprises the steps of:

20 (a) contacting said first set of small attached oligonucleotide probes with said intermediate length nucleic acid fragments under hybridization conditions effective to allow only those fragments with a completely complementary sequence to hybridize to a probe, thereby forming primary complexes wherein the fragment has hybridized and free sequences;

25 (b) contacting said primary complexes with said second set of small labelled oligonucleotide probes under hybridization conditions effective to allow only those probes with completely complementary sequences to hybridize to a free fragment sequence, thereby forming secondary complexes wherein the fragment is hybridized to an attached probe and a labelled probe;

30 (c) removing from said secondary complexes labelled probes that are not immediately adjacent to an

- 74 -

attached probe, thereby leaving only adjacent secondary complexes;

- 5 (d) detecting said adjacent secondary complexes by detecting the presence of the label; and
- 10 (e) identifying sequences from the nucleic acid fragments in said adjacent secondary complexes by connecting the known sequences of the hybridized attached and labelled probes.

12. A method of nucleic acid sequencing comprising the steps of:

- 15 (a) fragmenting the nucleic acid to be sequenced to provide nucleic acid fragments of length T;
- 20 (b) preparing an array of immobilized oligonucleotide probes of known sequences and length F and a set of labelled oligonucleotide probes in solution of known sequences and length P, wherein $F + P \leq T$;
- 25 (c) contacting said array of immobilized oligonucleotide probes with said nucleic acid fragments under hybridization conditions effective to allow the formation of primary complexes with hybridized, completely complementary sequences of length F and non-hybridized fragment sequences of length $T - F$;
- 30 (d) contacting said complexes with said set of labelled oligonucleotide probes under hybridization conditions effective to allow only the formation of secondary complexes with hybridized, completely complementary sequences

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of length F and immediately adjacent hybridized, completely complementary sequences of length P;

- 5 (e) detecting said secondary complexes by detecting the presence of the label;
- 10 (f) identifying sequences of length $F + P$ from the nucleic acid fragments in said secondary complexes by combining the known sequences of the hybridized immobilized and labelled probes;
- 15 (g) determining stretches of said sequences of length $F + P$ that overlap; and
- 16 (h) assembling the complete nucleic acid sequence from said overlapping sequences.

20 13. The method of claim 12, wherein length T is about three times longer than length F.

25 14. The method of claim 12, wherein length T is between about 10 nucleotides and about 40 nucleotides, length F is between about 4 nucleotides and about 9 nucleotides and length P is between about 4 nucleotides and about 9 nucleotides.

30 15. The method of claim 14, wherein length T is about 20 nucleotides, length F is about 6 nucleotides and length P is between about 6 nucleotides.

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16. / The method of claim 12, wherein said immediately adjacent immobilized and labeled oligonucleotide probes are ligated.

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17. A method of nucleic acid sequencing comprising the steps of:

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(a) fragmenting the nucleic acid to be sequenced to provide intermediate length nucleic acid fragments;

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(b) contacting an array of immobilized small oligonucleotide probes of known sequences with said nucleic acid fragments under hybridization conditions effective to allow only those fragments with a completely complementary sequence to hybridize to a probe, thereby forming primary complexes wherein the fragment has hybridized and non-hybridized sequences;

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(c) contacting said primary complexes with a set of labelled small oligonucleotide probes in solution of known sequences under hybridization conditions effective to allow only those probes with completely complementary sequences to hybridize to a non-hybridized fragment sequence, thereby forming secondary complexes wherein the fragment is hybridized to an immobilized probe and a labelled probe;

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(d) removing from said secondary complexes labelled probes that are not immediately adjacent to an immobilized probe, thereby leaving only adjacent secondary complexes;

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(e) detecting said adjacent secondary complexes by detecting the presence of the label;

5 (f) identifying sequences from the nucleic acid fragments in said adjacent secondary complexes by combining the known sequences of the hybridized immobilized and labelled probes;

10 (g) determining stretches of said sequences that overlap; and

(h) assembling the complete nucleic acid sequence from said overlapping sequences identified.

15 18. The method of claim 17, wherein the nucleic acid is cloned DNA or chromosomal DNA.

20 19. The method of claim 17, wherein the nucleic acid is mRNA.

25 20. The method of claim 17, wherein the nucleic acid is fragmented by restriction enzyme digestion, ultrasound treatment, NaOH treatment or low pressure shearing.

30 21. The method of claim 17, wherein the nucleic acid fragments are between about 10 nucleotides and about 100 nucleotides in length.

35 22. The method of claim 17, wherein the oligonucleotide probes are between about 4 nucleotides and about 9 nucleotides in length.

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23. The method of claim 22, wherein the oligonucleotide probes are about 6 nucleotides in length.
- 5 24. The method of claim 17, wherein said immobilized oligonucleotides are attached to a glass, polystyrene or teflon solid support.
- 10 25. The method of claim 17, wherein said immobilized oligonucleotides are attached to a solid support via a phosphodiester linkage.
- 15 26. The method of claim 17, wherein said immobilized oligonucleotides are attached to a solid support via a light-activated synthetic mechanism.
- 20 27. The method of claim 17, wherein the labelled oligonucleotide probes are labelled with a non-radioactive isotope or a fluorescent dye.
- 25 28. The method of claim 17, wherein the labelled oligonucleotide probes are labelled with ^{35}S , ^{32}P or ^{33}P .
- 30 29. The method of claim 17, wherein said nucleic acid fragment or one of said oligonucleotide probes contains a modified base or a universal base.
- 35 30. The method of claim 17, wherein labelled probes that are not immediately adjacent to an immobilized probe are removed from the secondary complexes by stringent washing conditions.

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31. The method of claim 17, wherein labelled probes that are immediately adjacent to an immobilized probe are ligated to said immobilized probe and non-ligated labelled probes are subsequently removed by washing.

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32. The method of claim 31, wherein said adjacent probes are ligated enzymatically.

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33. The method of claim 17, wherein multiple arrays of immobilized oligonucleotides are arranged in the form of a sequencing chip.

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34. A method of nucleic acid sequencing comprising the steps of:

20 (a) fragmenting the nucleic acid to be sequenced to provide nucleic acid fragments of between about 10 nucleotides and about 40 nucleotides in length;

25 (b) contacting an array of immobilized oligonucleotide probes with known sequences of between about 4 nucleotides and about 9 nucleotides in length with said nucleic acid fragments under hybridization conditions effective to allow only those fragments with a completely complementary sequence to hybridize to a probe, thereby forming primary complexes wherein the fragment has hybridized and non-hybridized sequences;

30 (c) contacting said complexes with a set of ^{32}P -labelled or ^{33}P -labelled oligonucleotide probes with known sequences of between about

- 80 -

4 nucleotides and about 9 nucleotides in length under hybridization conditions effective to allow only those labelled probes with completely complementary sequences to hybridize to a non-hybridized fragment sequence, thereby forming secondary complexes wherein the fragment is hybridized to an immobilized probe and a ^{32}P -labelled or ^{33}P -labelled probe;

- 5
- 10 (d) ligating the immobilized probes and labelled probes that are immediately adjacent with a DNA ligase enzyme, thereby forming ligated secondary complexes;
- 15 (e) removing from the secondary complexes any non-ligated labelled probes;
- (f) detecting said ligated secondary complexes by detecting the presence of the ^{32}P or ^{33}P label;
- 20 (g) identifying sequences from the nucleic acid fragments in said ligated secondary complexes by combining the known sequences of the ligated probes;
- 25 (h) determining stretches of said sequences that overlap; and
- (i) assembling the complete nucleic acid sequence from said overlapping sequences.
- 30

35. A kit for use in nucleic acid sequencing, comprising a solid support chip having attached an arrangement of oligonucleotide probes of known sequences, said oligonucleotides being capable of taking part in hybridization reactions, and a set of containers

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comprising solutions of labelled oligonucleotide probes of known sequences.

36. The kit of claim 35, wherein multiple chips of
5 immobilized oligonucleotide probes are arranged in the form of a sequencing array.

37. The kit of claim 35, wherein the oligonucleotide
10 probes are between about 4 nucleotides and about 9 nucleotides in length.

38. The kit of claim 37, wherein the oligonucleotide
15 probes are about 6 nucleotides in length.

39. The kit of claim 35, wherein the oligonucleotide
probes are attached to a glass, polystyrene or teflon
20 solid support.

40. The kit of claim 35, wherein the oligonucleotide
probes are attached to a solid support via a
25 phosphodiester linkage.

41. The kit of claim 35, wherein the oligonucleotide
probes are attached to a solid support via a light-
30 activated synthetic mechanism.

42. The kit of claim 35, wherein the labelled
oligonucleotide probes are labelled with a non-
35 radioactive isotope or a fluorescent dye.

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43. The kit of claim 35, wherein one of the oligonucleotide probes contains a modified or a universal base.

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44. The kit of claim 35, wherein the labelled oligonucleotide probes are labelled with ^{35}S , ^{32}P or ^{33}P .

10 45. The kit of claim 35, further comprising a ligating agent.

15 46. The kit of claim 45, wherein the ligating agent is a DNA ligase enzyme.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

08.11.95

Applicant's or agent's file reference
A21911PC

IMPORTANT NOTIFICATION

International application No.
PCT/US 94/ 10945

International filing date (day/month/year)
27/09/1994

Priority date (day/month/year)
27/09/1993

Applicant

ARCH DEVELOPMENT CORP. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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PATENT COOPERATION TREATY

PCT**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A21911PC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/ US 94/ 10945	International filing date (<i>day/month/year</i>) 27/09/1994	Priority date (<i>day/month/year</i>) 27/09/1993
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant ARCH DEVELOPMENT CORP. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

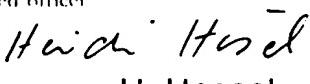
2. This REPORT consists of a total of 7 sheets, including this cover sheet.

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3. This report contains indications and corresponding pages relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 25/04/1995	Date of completion of this report 08.11.95
Name and mailing address of the IPEA:  European Patent Office D-80298 Munich Tel. (+49 89) 2399-0, Tx. 523656 epomu d Fax: (+49 89) 2399-4465	Authorized officer  H. Hoesel Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/US94/10945

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

[] the international application as originally filed.

[x] the description, pages 1 - 63, 67 - 70 _____, as originally filed,
pages 64 - 66 _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

[x] the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1 - 48 _____, filed with the letter of 11.10.95,
Nos. _____, filed with the letter of _____,

[x] the drawings, sheets/fig 1/5 - 5/5 _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[] the description, pages _____.
[] the claims, Nos. _____.
[] the drawings, sheets/fig _____.

3. [] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

The content of new Fig 3B has been changed with respect to the original figure sheet. The scheme given now in Fig 3B is inconsistent with the legend thereto given of p.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/US94/10945

19, lines 30 - 35, contrary to Art. 6 and 41(2) PCT.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/US94/10945

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N) Claims 1 - 48 _____ YES
 Claims _____ NO

Inventive Step (IS) Claims 1 - 48 _____ YES
 Claims _____ NO

Industrial Applicability (IA) Claims 1 - 48 _____ YES
 Claims _____ NO

2. CITATIONS AND EXPLANATIONS

1. The claimed method is distinguished from the closest prior art according to K.R.Khrapko et al, J DNA Sequencing and Mapping 1/3, 1990, p. 375 - 388 in that Continuous Stacking Hybridization ("CSH") is used alone for sequencing and in the additional ligation of the stacked oligonucleotide probes. Likewise the claimed kits comprise a ligating agent as an essential component.

The claimed subject-matter thus fulfils the requirement of novelty (Art. 33(2) PCT in the light of the available state of the art.

2. Modification of the CSH procedure according to the above document by an additional ligation step is not derivable from any of the available prior art documents. Consequently the methods and kits according to claims on file involves an inventive step (Art. 33(3) PCT.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

1. The requirements of Rule 5.1(a)(ii) PCT are not met, as the relevant content of document D concerning continuous stacking hybridization as a sequencing technique which represents a relevant background art is not acknowledged in the description.

2. The general statement in the description at page 28, lines 28 - 33, p. 62, line 28 - p. 63, line 6 is not clear, and when used to interpret the claims renders them also unclear, contrary to Article 6 PCT.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. The various definitions of the invention given in independent Claims 1, 3/11, 12, 17 and 34 are such that the claims as a whole are not clear and concise, contrary to Article 6 PCT. The claims should be recast to include only the minimum necessary number of independent claims in any one category (see below), with dependent claims as appropriate (Rule 6.4(a)-(c) PCT).
2. Having regard to the description, it appears that the following steps and procedural features are essential of the sequencing method according to the present application:
 - (a) Incubation of the target nucleic acid (optionally fragmented into stretches of suitable length) with a first set of oligonucleotide probes (oligonucleotide library comprising all 4ⁿ probe sequences, n representing the number of nucleotides of the probes), which
 - (b) are immobilized in a predetermined array on a solid support material ("DNA-chip"),
 - (c) under stringent conditions that allow hybridization of completely complementary sequences only
 - (d) incubation of the target nucleic acid hybridized to the solid phase(s) under likewise stringent conditions with a set of labelled probe oligonucleotides (either simultaneously or in a sequential manner) whereby
 - (d) each DNA chip is reacted with 1 probe species only

and

(e) The performance of a "discriminatory washing step" that removes probes which are not ligated to the immobilized probe.

It would appear that only the combination of all these procedural feature permits the successful sequencing of nucleic acids.

Since method claims 1, 3, 11, 12, 17 and 34 lack at least one of these essential procedural features, they do not fulfil the requirements of Art. 6 PCT.

3. Claim 35 seems to lack essential technical features, too, contrary to Art. 6 PCT.

In order to be suited for performance of the method according to the present application the chip apparently has to contain all 4ⁿ possible probes (representing said "first set" of oligos) each being of identical length (if. p. 23, 3rd paragraph). Likewise the kit apparently would have to contain a complete library of labelled probes contained in separate containers.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/12305

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 810; 536/22.1, 23.1, 24.3, 24.31, 24.32, 24.33, 25.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,656,127 (MUNDY) 07 April 1987, see especially figure 8 and example 2 in columns 10-13.	1, 7-11, 18, 28, 29, 52, 53, 60, 61, 63
Y		----- 2-6, 12-17, 19- 27, 30-36, 47- 51, 54-59, 62, 64-84

Further documents are listed in the continuation of Box C. See patent family annex.

Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

13 FEBRUARY 1995

Date of mailing of the international search report

02 MAR 1995

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/12305

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A, 92/10588 (FODOR ET AL.) 25 June 1992, see the entire disclosure, especially the abstract.	1-36, 47-64
—		-----
Y		65-84
Y	Nature, Volume 313, issued 24 January 1985, Ratner et al., "Complete nucleotide sequence of the AIDS virus, HTLV-III", pages 277-284, see the entire disclosure.	65-84
Y	Virology, Volume 175, issued 1990, Querat et al., "Nucleotide Sequence Analysis of SA-OMVV, a Visna-Related Ovine Lentivirus: Phylogenetic History of Lentiviruses", pages 434-447.	64-70, 72-84
Y,P	Journal of Virology, Volume 68, Number 6, issued June 1994, Luo et al., "Cellular Protein Modulates Effects of Human Immunodeficiency Virus Type 1 Rev", pages 3850-3856, see the abstract.	64-69, 71-84
Y	Cell, Volume 40, issued January 1985, Wain-Hobson et al., "Nucleotide Sequence of the AIDS Virus, LAV", pages 9-17, see the entire disclosure.	65-84
Y	Journal of Biomolecular Structure & Dynamics, Volume 11, Number 3, issued 1993, Lipshutz, "Likelihood DNA Sequencing By Hybridization", pages 637-653, see the entire disclosure and especially the abstract.	1-36, 47-84
Y	Maximum Entropy and Bayesian Methods (Paris), issued 1992, Elder, "Analysis of DNA Oligonucleotide Hybridization Data by Maximum Entropy", pages 1-10, see especially the abstract and the discussion relating to Figure 2 on page 6.	1-36, 47-84
Y	WO, A, 89/10977 (SOUTHERN) 16 November 1989, see especially the abstract and claims 1-14.	1-36, 47-84
X	Genomics, Volume 13, issued 1992, Southern et al., "Analyzing and Comparing Nucleic Acid Sequences by Hybridization to Arrays of Oligonucleotides: Evaluation Using Experimental Models", pages 1008-1017, see especially the abstract and Figures 2-4 on pages 1010-1012.	1-36, 47-64
—		-----
Y		65-84
X	WO, A, 93/17126 (CHETVERIN ET AL.) 02 September 1993, see especially the abstract and claims 1-197.	1-36, 47-64
—		-----
Y		65-84

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/12305

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	US, A, 5,002,867 (MACEVICZ) 26 March 1991, see especially the abstract and claims 1-23.	1-36, 47-64 -----
Y		65-84
X ---	US, A, 5,202,231 (DRMANAC ET AL.) 13 April 1993, see especially the abstract and claims 1-4.	1-36, 47-64 -----
Y		65-84

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/12305

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-36 and 47-84

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US94/12305**A. CLASSIFICATION OF SUBJECT MATTER:**
IPC (6):

C12Q 1/68; C07H 21/02, 21/04

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/6; 536/22.1, 23.1, 24.3, 24.31, 24.32

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

CAS, BIOSIS, WORLD PATENT INDEX, BIOTECH ABS., MEDLINE

search terms: probes, arrays, hybridization, matrix, sequencing, probe set

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-36 and 47-84, drawn to arrays of oligonucleotide probes including specifically HIV directed arrays and methods of using said arrays via hybridization to target nucleic acid.

Group II, claims 37-41, drawn to methods of using arrays of pools of probes for the comparison of a target sequence with a reference sequence.

Group III, claims 42-46, drawn to pooled probes and arrays of pooled probes immobilized on a solid support.

Group IV, claims 85-96, drawn to arrays directed to reference sequences directed to the CFTR gene.

Group V, claims 97, 98, and 100-103, drawn to arrays directed to reference sequences directed to the p53 and hMLH1 genes.

Group VI, claim 99, drawn to arrays directed to reference sequences directed to the MSH2 gene.

Group VII, claims 104-108, drawn to arrays directed to reference sequences directed to sequences from the mitochondrial genome.

The inventions listed as Groups I-VII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The arrays and methods of use in the invention of Group I utilize probe sets having interrogation positions therein where hybridization of the target nucleic acid to certain probes results in determining whether the target nucleic acid is the same or different from the reference sequence. Certain claims are directed specifically to HIV reference sequences. The special technical feature is deemed to be the practice of probe sets wherein specific hybridization to certain probes produces an indication of whether the interrogation position is the same or different from the reference sequence wherein the target sequence is determined by the compilation of interrogation sequence results to obtain the entire sequence. The first claimed specific reference sequence is directed to HIV. In contrast, Groups II and III cite the practice of pooled probes with variant sequences therein which are exactly complementary to each variant target sequence. The intensity of hybridization to each pool is the manner of determining the comparison between the target nucleic acid and the reference sequence. Groups II and III therefore do not determine the target sequence using the special technical features cited above but instead signal intensity using pooled probes. Therefore unity of invention is lacking between Group I and Groups II and III. Groups II and III also lack unity of invention with each other because Group II is directed to methods of using Group II is directed to the use of arrays of pooled probes whereas Group III is

ARCH DEVELOPMENT CORPORATION

October 11, 1995
A21911PC DO/AD/al/cp

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CLAIMS

1. A method for determining the sequence of a nucleic acid molecule,
10 comprising the steps of:
 - (a) identifying sequences from the molecule by:
 - (i) hybridizing the molecule to complementary sequences of oligonucleotides from two sets of small oligonucleotide probes of known sequence, wherein the first set of probes are attached to a solid support and the second set of probes are labelled probes in solution; and
 - 15 (ii) covalently bonding a hybridized oligonucleotide from said first set of probes to a hybridized oligonucleotide from said second set of probes;
 - (b) identifying overlapping stretches of sequence from the sequences identified in step (a); and
 - 25 (c) assembling the nucleic acid sequence of the molecule from said overlapping sequences identified.
- 30 2. The method of claim 1, wherein said hybridization is carried out in cycles.

3. A method for determining the sequence of a nucleic acid molecule, comprising the steps of:
 - (a) fragmenting the nucleic acid molecule to be sequenced to provide intermediate length nucleic acid fragments;
 - (b) identifying sequences from said fragments by:
 - (i) hybridizing the fragments to complementary sequences of oligonucleotides from two sets of small oligonucleotides probes of known sequence, wherein the first set of probes are attached to a solid support and the second set of probes are labelled probes in solution; and
 - (ii) covalently bonding a hybridized oligonucleotide from said first set of probes to a hybridized oligonucleotide from said second set of probes;
 - (c) identifying overlapping stretches of sequence from said sequences identified in step (b); and
 - (d) assembling the nucleic acid sequence of the molecule from said overlapping sequences identified.
4. The method of claim 3, wherein said fragments are sequentially hybridized to complementary sequences from two sets of small oligonucleotide probes of known sequence.

5. The method of claim 3, wherein said fragments are simultaneously hybridized to complementary sequences from two sets of small oligonucleotide probes of known sequence.
- 5 6. The method of claim 3, wherein said intermediate length nucleic acid fragments are between about 10 nucleotides and about 40 nucleotides in length and said small oligonucleotides probes are between about 4 nucleotides and about 9 nucleotides in length.
- 10 7. The method of claim 3, wherein said oligonucleotide probes hybridize to completely complementary sequences from said fragments.
8. The method of claim 3, wherein said oligonucleotide probes hybridize to immediately adjacent sequences from said fragments.
- 15 9. The method of claim 8, wherein said oligonucleotide probes hybridize to completely complementary and immediately adjacent sequences from said fragments.
- 20 10. The method of claim 3, wherein said oligonucleotide probes are covalently bonded by enzymatic ligation.
11. The method of claim 3, wherein said oligonucleotide probes are covalently bonded using a chemical ligating agent.
- 25 12. The method of claim 3, wherein step (b) comprises the steps of:
 - (a) contacting said first set of small attached oligonucleotide probes with said intermediate length nucleic acid fragments under hybridization conditions effective to allow only those fragments

with a completely complementary sequence to hybridize to a probe, thereby forming primary complexes wherein the fragment has hybridized and free sequences;

- 5 (b) contacting said primary complexes with said second set of small labelled oligonucleotide probes under hybridization conditions effective to allow only those probes with completely complementary sequences to hybridize to a free fragment sequence, thereby forming secondary complexes wherein the fragment is hybridized to an attached probe and a labelled probe;
- 10 (c) covalently bonding said attached probe and said labelled probe;
- 15 (d) removing from said secondary complexes labelled probes that are not covalently bonded to an attached probe, thereby forming covalently bonded complexes;
- 20 (e) detecting said covalently bonded complexes by detecting the presence of the label; and
- (f) identifying sequences from the nucleic acid fragments in said covalently bonded complexes by connecting the known sequences of the hybridized attached and labelled probes.

25 13. A method of nucleic acid sequencing comprising the steps of:

- (a) fragmenting the nucleic acid to be sequenced to provide nucleic acid fragments of length T;

(b) preparing an array of immobilized oligonucleotide probes of known sequences and length F and a set of labelled oligonucleotide probes in solution of known sequences and length P, wherein $F + P \leq T$;

5

(c) contacting said array of immobilized oligonucleotide probes with said nucleic acid fragments under hybridization conditions effective to allow the formation of primary complexes with hybridized, completely complementary sequences of length F and non-hybridized fragment sequences of length $T - F$;

10

(d) contacting said complexes with said set of labelled oligonucleotide probes under hybridization conditions effective to allow only the formation of secondary complexes with hybridized, completely complementary sequences of length F and immediately adjacent hybridized, completely complementary sequences of length P;

15

(e) covalently bonding said labelled oligonucleotide probes to said immediately adjacent immobilized oligonucleotide probes;

20

(f) detecting said secondary complexes by detecting the presence of the label;

25

(g) identifying sequences of length $F + P$ from the nucleic acid fragments in said secondary complexes by combining the known sequences of the hybridized immobilized and labelled probes;

30

(h) determining stretches of said sequences of length $F + P$ that overlap; and

- (i) assembling the complete nucleic acid sequence from said overlapping sequences.
14. The method of claim 13, wherein length T is about three times
5 longer than length F.
15. The method of claim 13, wherein length T is between about 10 nucleotides and about 40 nucleotides, length F is between about 4 nucleotides and about 9 nucleotides and length P is between about
10 4 nucleotides and about 9 nucleotides.
16. The method of claim 15, wherein length T is about 20 nucleotides, length F is about 6 nucleotides and length P is about 6 nucleotides.
- 15 17. The method of claim 13, wherein said immediately adjacent immobilized and labelled oligonucleotide probes are covalently bonded by enzymatic ligation.
- 20 18. The method of claim 13, wherein said immediately adjacent immobilized and labelled oligonucleotide probes are covalently bonded using a chemical ligating agent.
19. A method of nucleic acid sequencing comprising the steps of:
25 (a) fragmenting the nucleic acid to be sequenced to provide intermediate length nucleic acid fragments;
- (b) contacting an array of immobilized small oligonucleotide probes of known sequences with said nucleic acid fragments under hybridization conditions effective to allow only those fragments
30

with a completely complementary sequence to hybridize to a probe, thereby forming primary complexes wherein the fragment has hybridized and non-hybridized sequences;

- 5 (c) contacting said primary complexes with a set of labelled small oligonucleotide probes in solution of known sequences under hybridization conditions effective to allow only those probes with completely complementary sequences to hybridize to a non-hybridized fragment sequence, thereby forming secondary complexes wherein the fragment is hybridized to an immobilized probe and a labelled probe;
- 10 (d) covalently bonding said labelled oligonucleotide probes to said immediately adjacent immobilized oligonucleotide probes;
- 15 (e) removing from said secondary complexes labelled probes that are not covalently bonded to an immobilized probe, thereby forming covalently bonded complexes;
- 20 (f) detecting said covalently bonded complexes by detecting the presence of the label;
- 25 (g) identifying sequences from the nucleic acid fragments in said covalently bonded complexes by combining the known sequences of the hybridized immobilized and labelled probes;
- 30 (h) determining stretches of said sequences that overlap; and
- (i) assembling the complete nucleic acid sequence from said overlapping sequences identified.

20. The method of claim 19, wherein the nucleic acid is cloned DNA or chromosomal DNA.
21. The method of claim 19, wherein the nucleic acid is mRNA.
5
22. The method of claim 19, wherein the nucleic acid is fragmented by restriction enzyme digestion, ultrasound treatment, NaOH treatment or low pressure shearing.
- 10 23. The method of claim 19, wherein the nucleic acid fragments are between about 10 nucleotides and about 100 nucleotides in length.
24. The method of claim 19, wherein the oligonucleotide probes are between about 4 nucleotides and about 9 nucleotides in length.
15
25. The method of claim 24, wherein the oligonucleotide probes are about 6 nucleotides in length.
26. The method of claim 19, wherein said immobilized oligonucleotides
20 are attached to a glass, polystyrene or teflon solid support.
27. The method of claim 19, wherein said immobilized oligonucleotides are attached to a solid support via a phosphodiester linkage.
- 25 28. The method of claim 19, wherein said immobilized oligonucleotides are attached to a solid support via a light-activated synthetic mechanism.
29. The method of claim 19, wherein the labelled oligonucleotide probes
30 are labelled with a non-radioactive isotope or a fluorescent dye.

30. The method of claim 19, wherein the labelled oligonucleotide probes are labelled with ^{35}S , ^{32}P or ^{33}P .
31. The method of claim 19, wherein said nucleic acid fragment or one of said oligonucleotide probes contains a modified base or a universal base.
5
32. The method of claim 19, wherein labelled probes that are not covalently bonded to an immobilized probe are removed from the secondary complexes by stringent washing conditions.
10
33. The method of claim 19, wherein said immediately adjacent probes are chemically bonded.
- 15 34. The method of claim 19, wherein said immediately adjacent probes are ligated enzymatically.
35. The method of claim 19, wherein multiple arrays of immobilized oligonucleotides are arranged in the form of a sequencing chip.
20
36. A method of nucleic acid sequencing comprising the steps of:
 - (a) fragmenting the nucleic acid to be sequenced to provide nucleic acid fragments of between about 10 nucleotides and about 40 nucleotides in length;
25
 - (b) contacting an array of immobilized oligonucleotide probes with known sequences of between about 4 nucleotides and about 9 nucleotides in length with said nucleic acid fragments under hybridization conditions effective to allow only those fragments
30

with a completely complementary sequence to hybridize to a probe, thereby forming primary complexes wherein the fragment has hybridized and non-hybridized sequences;

- 5 (c) contacting said complexes with a set of ^{32}P -labelled or ^{33}P -labelled oligonucleotide probes with known sequences of between about 4 nucleotides and about 9 nucleotides in length under hybridization conditions effective to allow only those labelled probes with completely complementary sequences to hybridize to a non-hybridized fragment sequence, thereby forming secondary complexes wherein the fragment is hybridized to an immobilized probe and a ^{32}P -labelled or ^{33}P -labelled probe;
- 10 (d) ligating the immobilized probes and labelled probes that are immediately adjacent with a DNA ligase enzyme, thereby forming ligated secondary complexes;
- 15 (e) removing from the secondary complexes any non-ligated labelled probes;
- 20 (f) detecting said ligated secondary complexes by detecting the presence of the ^{32}P or ^{33}P label;
- 25 (g) identifying sequences from the nucleic acid fragments in said ligated secondary complexes by combining the known sequences of the ligated probes;
- (h) determining stretches of said sequences that overlap; and

- (i) assembling the complete nucleic acid sequence from said overlapping sequences.
37. A kit for use in nucleic acid sequencing, comprising a solid support chip having attached an arrangement of oligonucleotide probes of known sequences, said oligonucleotides being capable of taking part in hybridization reactions, a set of containers comprising solutions of labelled oligonucleotide probes of known sequences, and a ligating agent.
- 10 38. The kit of claim 37, wherein multiple chips of immobilized oligonucleotide probes are arranged in the form of a sequencing array.
- 15 39. The kit of claim 37, wherein the oligonucleotide probes are between about 4 nucleotides and about 9 nucleotides in length.
40. The kit of claim 39, wherein the oligonucleotide probes are about 6 nucleotides in length.
- 20 41. The kit of claim 37, wherein the oligonucleotide probes are attached to a glass, polystyrene or teflon solid support.
42. The kit of claim 37, wherein the oligonucleotide probes are attached to a solid support via a phosphodiester linkage.
- 25 43. The kit of claim 37, wherein the oligonucleotide probes are attached to a solid support via a light-activated synthetic mechanism.
44. The kit of claim 37, wherein the labelled oligonucleotide probes are labelled with a non-radioactive isotope or a fluorescent dye.
- 30

45. The kit of claim 37, wherein one of the oligonucleotide probes contains a modified or a universal base.
46. The kit of claim 37, wherein the labelled oligonucleotide probes are
5 labelled with ^{35}S , ^{32}P or ^{33}P .
47. The kit of claim 37, wherein said ligating agent is a chemical ligating agent.
- 10 48. The kit of claim 37, wherein the ligating agent is a DNA ligase enzyme.

25 APR 1995

REPLACEMENT SHEET

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details
5 supplementary to those set forth herein, are specifically incorporated herein by reference.

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25 APR 1995

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

DOST, Wolfgang
BARDEHLE, DOST, ALtenburg
et al
Galileiplatz 1 -
81679 München
ALLEMAGNE

WRITTEN OPINION

(PCT Rule 66)

*11.10.95 not
11.09.95 not*

Date of mailing
(day/month/year)

11 JUL 1995

Applicant's or agent's file reference
A21911PC

REPLY DUE

within **3** months/days
from the above date of mailing

International application No.
PCT/US 94/ 10945

International filing date (day/month/year)
27/09/1994

Priority date (day/month/year)
27/09/1993

International Patent Classification (IPC) or both national classification and IPC:

C12Q1/68

Applicant

ARCH DEVELOPMENT CORP. et al.

1. This written opinion is the first (first, etc.) drawn up by this International Preliminary Examining Authority.

2. This report contains indications and corresponding pages relating to the following items:

- I Basis of the opinion
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 27/01/1996

Name and mailing address of the IPEA:



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Fax: 523656 epmu d
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Authorized officer

Examiner

H. Hoesel

H. Hoesel

Formalities officer
(incl. extension of time limits)
Telephone No.

Peter Ehrenreich

WRITTEN OPINION

I. Basis of the opinion

1. This opinion has been drawn up on the basis of (Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".):

[] the international application as originally filed.

[x] the description, pages 1 - 63 _____, as originally filed,
pages 64 - 66 _____, filed with the demand,
pages _____, filed with the letter of _____,

[x] the claims, Nos. 1 - 46 _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,

[x] the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig 1/5 - 5/5 _____, filed with the letter of 08.12.94,

2. The amendments have resulted in the cancellation of:

[] the description, pages _____.
[] the claims, Nos. _____.
[] the drawings, sheets/fig _____.

3. [] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

The content of new Fig 3B has been changed with respect to the original figure sheet. The scene given now in Fig 3B is inconsistent with the legend thereto given of p. 19, lines 30 - 35.

The applicant is requested to file a corrected figure sheet.

WRITTEN OPINION

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1 - 46 (yes) _____ Claims _____
Inventive Step (IS)	Claims 1 - 9, 11 - 15, 17 - 30, 33, 35 - 44 (no) _____ Claims 10, 16, 31, 32, 34, 45, 46 (yes) _____
Industrial Applicability (IA)	Claims 1 - 46 (yes) _____ Claims _____

2. CITATIONS AND EXPLANATIONS

The closest prior art for the present subject-matter is provided by

D: K.R.Khrapko et al, J DNA Sequence and Mapping 1/3, 1990, p. 375 - 388.

Besides SBH sequencing according to format 2, said document describes the use of "continuous stacking hybridization (CSH)" for the sequence analysis of nucleic acids (p. 385, left-hand column, 2nd paragraph - 2nd paragraph on p. 386 as well as Figs. 8 and 9).

D = document

According to D, CSH may be performed using a DNA chip and a library of labelled oligonucleotides (of 3 - 5 nucleotides in length. In said document it is particularly pointed to the efficiency of this method in sequence analysis where conventional format 2 SBH fails (see e.g.. p. 385, col. 1, l. 15 - 19, 40 - col. 2, line 8, same col., line 22, p. 386, col 1, line 14). However,

WRITTEN OPINION

according to D, the CSH is proposed of being used in addition to format 2 sequencing in those instances where the sequencing by format 2 does not allow an unambiguous sequence analysis.

Thus the present sequencing method relying upon CSH only would appear to be novel in the light of the teaching of D. However, having regard to the advantages of increased sequencing accuracy, a skilled person would regard the performance of CSH alone for sequencing unknown nucleic acid as an obvious alternative. Consequently, the method as covered by claims 1 - 9, 11 - 15, 17 - 30 and 33 would not appear to fulfil the requirements of Art. 33(3) PCT.

2. The subject-matter of claims 35 - 46 does not fulfil the requirements of Art. 33(3) PCT either.

Even if the method according to D appears to differ from the present one, it is said to require (a) a DNA chip containing a immobilized oligonucleotide library and - for performing additional CSH hybridizations - a library of labelled oligonucleotides (e.g. all 1024 possible pentanucleotides).

The preparation of kits is common knowledge in the pertaining technical field. Thus, a skilled person would regard the preparation of kits for carrying out the method described in D as obvious and a matter of design. In this instance he would automatically arrive at the subject-matter of claims 35 - 39.

Claims 40 - 44 recite features which are common design options in the technical field of DNA fixation and labelling. They would not infer an inventive activity to the independent claim when incorporated therein.

WRITTEN OPINION

3. The stabilization of adjacently hybridized probes by ligation prior to washing is not disclosed or suggested in the relevant background art. It would therefore appear that incorporation of the features of claim 45 into the corresponding independent claim yield patentable novel and inventive subject-matter as required under Art. 33(2) and 33(3) PCT.

Analogously, claim 34 would appear to fulfil the requirements of Art. 33(2) and 33(3) PCT (but please see Section VIII)

WRITTEN OPINION

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

1. To meet the requirements of Rule 5.1(a)(ii) PCT, the relevant content of document D concerning continuous stacking hybridization as a sequencing technique which represents relevant background should be briefly discussed in the description.
2. The general statement in the description at page 28, lines 28 - 33, p. 62, line 28 p. 63 - line 6 is not clear, and when used to interpret the claims renders them also unclear, contrary to Article 6 PCT. The statement should therefore be deleted.

WRITTEN OPINION

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. The various definitions of the invention given in independent Claims 1, 3/11, 12, 17 and 34 are such that the claims as a whole are not clear and concise, contrary to Article 6 PCT. The claims should be recast to include only the minimum necessary number of independent claims in any one category (see below), with dependent claims as appropriate (Rule 6.4(a)-(c) PCT).
2. Having regard to the description, it appears that the following steps and procedural features are essential of the sequencing method according to the present application:
 - (a) Incubation of the target nucleic acid (optionally fragmented into stretches of suitable length) with a first set of oligonucleotide probes (oligonucleotide library comprising all 4^n probe sequences, n representing the number of nucleotides of the probes), which
 - (b) are immobilized in a predetermined array on a solid support material ("DNA-chip"),
 - (c) under stringent conditions that allow hybridization of completely complementary sequences only
 - (d) incubation of the target nucleic acid hybridized to the solid phase(s) under likewise stringent conditions with a set of labelled probe oligonucleotides (either simultaneously or in a sequential manner) whereby
 - (e) each DNA chip is reacted with 1 probe species only

WRITTEN OPINION

and

- (e) ^f The performance of a "discriminatory washing step" that removes probes which are not bound immediately adjacent to the immobilized probe.

It would appear that only the combination of all these procedural feature permits the successful sequencing of nucleic acids.

Since method claims 1, 3, 11, 12, 17 and 34 lack at least one of these essential procedural features, they do not fulfil the requirements of Art. 6 PCT.

3. Claim 35 seems to lack essential technical features, too, contrary to Art. 6 PCT.

In order to be suited for performance of the method according to the present application the chip apparently has to contain all 4ⁿ possible probes (representing said "first set" of oligos) each being of identical length (if. p. 23, 3rd paragraph). Likewise the kit apparently would have to contain a complete library of labelled probes contained in separate containers.



EPA / EPO / OEB
D - 80398 München
Tel. 089 - 2395 - 0
Fax. 089 - 2395 - 4465

Europäisches
Patentamt

European
Patent Office

Office européen
des brevets

Generaldirektion I

Directorate General I

Dirección general I

Schriftverkehr mit dem EPA bei PCT Kapitel II Anträgen

Um sicherzustellen, daß Ihr PCT Kapitel II Antrag so rasch wie möglich behandelt werden kann, werden Sie gebeten die beige-fügten Klebeschilder bei allen an das EPA München gerichteten Schriftstücken zu verwenden.

Eines dieser Klebeschilder sollte an gut erkennbarer Stelle am oberen Rand der Titelseite des jeweiligen Schreibens angebracht werden..

Correspondence with the EPO on PCT Chapter II demands

In order to ensure that your PCT Chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.

Correspondance avec l'OEB en ce qui concerne les demandes PCT, chapitre II

Pour être sûr que votre demande PCT, chapitre II, sera traitée aussi vite que possible, vous êtes pries d'utiliser les étiquettes autocollantes ci-jointes avec le courrier relatif à la demande envoyé à l'Office à Munich.

Une de ces étiquettes devrait être apposée à un endroit bien visible, à la partie supérieure de l'en-tête de la lettre ou du formulaire etc. que vous déposez.

PATENT COOPERATION TREATY

REC'D.-A.W.&L.

FEB 24 1995

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
 ARNOLD, WHITE & DURKEE
 Attn. PARKER, David L.
 750 Bering Drive , Suite 400
 HOUSTON, TEXAS 77057
 UNITED STATES OF AMERICA

RECEIVED
 NOTIFICATION OF TRANSMITTAL OF
 A.W & D. THE INTERNATIONAL SEARCH REPORT
 AUSTIN, INT'L OR THE DECLARATION

FEB 27 1995

(PCT Rule 44.1)

08/127420
 08/303058

P19713 AB
 P21295 ✓

US Case Docketed for IDS Due

Date of mailing
 (day/month/year)

17.02.95

Applicant's or agent's file reference
 ARCD146P--

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
 PCT/ US 94/ 10945

International filing date
 (day/month/year)

27/09/94

Applicant

ARCH DEVELOPMENT CORP. et al.

1. The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? To the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. With regard to the protest against payment of (an) additional fee(s) under Rule 40.2; the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority
 European Patent Office, P.B. 5818 Patentlaan 2
 NL-2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Ute Alef

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ARCD146P--	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/ US 94/ 10945	International filing date (<i>day/month/year</i>) 27/09/94	(Earliest) Priority Date (<i>day/month/year</i>) 27/09/93
Applicant ARCH DEVELOPMENT CORP. et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.
 It is also accompanied by a copy of each prior art document cited in this report.

1. Certain claims were found unsearchable (see Box I).
2. Unity of invention is lacking (see Box II).
3. The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - filed with the international application.
 - furnished by the applicant separately from the international application,
 - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - Transcribed by this Authority
4. With regard to the title, the text is approved as submitted by the applicant.
 the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - the text is approved as submitted by the applicant.
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 Figure No. 1ABC
 - as suggested by the applicant.
 - because the applicant failed to suggest a figure.
 - because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/10945

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. DNA SEQUENCE AND MAPPING, vol.1, no.3, 1990, HARWOOD ACADEMIC PUBLISHERS GMBH, UK; pages 375 - 388 K.R. KHRAPKO ET AL. 'A method for DNA sequencing by hybridization with oligonucleotide matrix' cited in the application see page 385, left column, line 14 - page 386, left column, line 14; figure 8 ---- -/-	1
Y		2-46

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

1

Date of the actual completion of the international search

10 February 1995

Date of mailing of the international search report

17.02.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl.
 Fax (+ 31-70) 340-3016

Authorized officer

Hornig, H

INTERNATIONAL SEARCH REPORT

National Application No

PCT/US 94/10945

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GENOMICS, vol.13, no.4, August 1992, ACADEMIC PRESS, NEW YORK, US; pages 1378 - 1383 C.R. CANTOR ET AL. 'Report on the sequencing by hybridization workshop' cited in the application see page 1379, left column, line 10 - line 26; figure 1 ----	1
Y	SCIENCE, vol.258, no.5089, 11 December 1992, AAAS, WASHINGTON, DC, US; pages 1787 - 1791 J. KIELECZAWA ET AL. 'DNA sequencing by primer walking with strings of contiguous hexamers' see page 1787, middle column, line 5 - line 16 ----	2-46
Y	GENE, vol.90, no.1, 31 May 1990, ELSEVIER PUBLISHERS, N.Y., U.S.; pages 177 - 178 W. SZYBALSKI 'Proposal for sequencing DNA using ligation of hexamers to generate sequential elongation primers (SPEL-6)' the whole document ----	2-46
Y	WO,A,93 05183 (BAYLOR COLLEGE OF MEDICINE) 18 March 1993 see page 6, line 7 - page 12, line 18; claims 1-26; figure 4 ----	2-46
Y	WO,A,91 06678 (SRI INTERNATIONAL) 16 May 1991 see page 10, line 19 - page 18, line 33; claims 1-50; figure 1 ----	2-46
A	SCIENCE, vol.260, 11 June 1993, AAAS, WASHINGTON, DC, US; pages 1649 - 1652 R. DRMANAC ET AL. 'DNA sequence determination by hybridization: A strategy for efficient large-scale sequencing' the whole document ----	1-46
A	US,A,5 202 231 (DRMANAC ET AL.) 13 April 1993 cited in the application the whole document ----	1-46
		-/-

INT'L INTERNATIONAL SEARCH REPORT

ational Application No

PCT/US 94/10945

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PROC. NATL. ACAD SCI., vol.86, September 1989, NATL. ACAD SCI., WASHINGTON, DC, US; pages 6917 - 6921 F.W. STUDIER 'A strategy for high-volume sequencing of cosmid DNAs: Random and directed priming with a library of oligonucleotides' the whole document</p> <p style="text-align: center;">---</p>	1-46
A	<p>FEBS LETT., vol.256, no.1,2, October 1989, ELSEVIER PUBLISHERS, AMSTERDAM, NL; pages 118 - 122 K.R. KHRAPKO ET AL. 'An oligonucleotide hybridization approach to DNA sequencing' the whole document</p> <p style="text-align: center;">-----</p>	1-46

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/10945

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9305183	18-03-93	AU-A-	2674092	05-04-93
WO-A-9106678	16-05-91	EP-A-	0450060	09-10-91
US-A-5202231	13-04-93	NONE		

PATENT COOPERATION TREATY

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

REC'D. - A. W. & D.

PARKER, David, L.
Arnold, White & Durkee
P.O. Box 4433
Houston, TX 77210

APR 17 1995

INTERNATIONAL DEPT.
ETATS-UNIS D'AMERIQUE

RECEIVED

A.W. & D.
ALISTIN. INT'LDate of mailing (day/month/year)
06 April 1995 (06.04.95)

APR 18 1995

IMPORTANT NOTICE

Applicant's or agent's file reference
ARCD146P--

International application No.

PCT/US94/10945

International filing date

27 September 1994 (27.09.94)

Priority date

27 September 1993 (27.09.93)

Applicant

ARCH DEVELOPMENT CORP. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AT,AU,BR,BY,CA,CN,CZ,DE,EP,ES,FI,GB,GE,HU,JP,KE,KG,KP,KR,KZ,LK,LT,LV,MD,MN,NL,NO,
NZ,PL,PT,RO,RU,SD,SK,TJ,UA,US,UZ,VN

2. In accordance with Rule 47.1(c), third sentence, each designated Office will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Offices.
3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on

06 April 1995 (06.04.95) under No. WO 95/09248

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

8 mo pub
4-6-95
J. Zahra

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer:

J. Zahra

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 730.91.11

707866

Continuation of Form PCT/IB/308

**NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF
THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES**

Date of mailing (day/month/year) 06 April 1995 (06.04.95)	IMPORTANT NOTICE
Applicant's or agent's file reference ARCD146P--	International application No. PCT/US94/10945
<p>The designated Office(s) of:</p> <p>AM,AP,BB,BG,CH,DK,LU,MG,MW,OA,SE,SI,TT</p> <p>has (have) waived the requirement for such a communication, but nevertheless a copy of the international application need not be furnished by the applicant to the Office(s) concerned.</p>	

PATENT COOPERATION TREATY

PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

RECEIVED

Date of mailing: A.W. & D.
26 May 1995 (26.05.95) AUSTIN, INTL

Applicant's or agent's file reference: JUN 07 1995
ARCD146P--

IMPORTANT INFORMATION

International application No.: PCT/US94/10945	International filing date: 27 September 1994 (27.09.94)	Priority date: 27 September 1993 (27.09.93)
--	--	--

Applicant:
ARCH DEVELOPMENT CORP. et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Office of its election:

AP :KE,MW,SD,SZ

EP :AT,BE,DE,DK,FR,GB,IE,IT,LU,MC,NL,PT,SE

OA :BF,BJ,CF,CG,CI,CM,GA,GN,ML,MR,NE,SN,TD,TG

National :AM,AT,AU,BB,BG,BR,BY,CA,CN,CZ,DE,DK,FI,GB,GE,HU,JP,KE,KG,KP,KR,
KZ,LK,LT,LU,LV,MD,MG,MN,MW,NL,NO,NZ,PL,PT,RO,RU,SD,SE,SI,SK,TJ,TT,UA,US,
UZ,VN

The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of the annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent including, where applicable CH & LI, ES and GR, which cannot be elected since they are not bound by Chapter II.

REC'D. - A. W. & D.

JUN - 6 1995

INTERNATIONAL DEPT.

DOCKETED UPDATED
Previously _____ Not Required
Action Required: _____

DATE DUE: _____
Cl. _____ Cl. _____

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

Schmitt

B. Schmitt

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ARCD146P--	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/ US 94/ 10945	International filing date (<i>day/month/year</i>) 27/09/94	(Earliest) Priority Date (<i>day/month/year</i>) 27/09/93
Applicant ARCH DEVELOPMENT CORP. et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Certain claims were found unsearchable (see Box I).
2. Unity of invention is lacking (see Box II).
3. The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - filed with the international application.
 - furnished by the applicant separately from the international application,
 - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - Transcribed by this Authority
4. With regard to the title,
 - the text is approved as submitted by the applicant
 - the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - the text is approved as submitted by the applicant
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 - Figure No. 1ABC
 - as suggested by the applicant.
 - because the applicant failed to suggest a figure.
 - because this figure better characterizes the invention.
 - None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/10945

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. DNA SEQUENCE AND MAPPING, vol.1, no.3, 1990, HARWOOD ACADEMIC PUBLISHERS GMBH, UK; pages 375 - 388 K.R. KHRAPKO ET AL. 'A method for DNA sequencing by hybridization with oligonucleotide matrix' cited in the application see page 385, left column, line 14 - page 386, left column, line 14; figure 8 ---	1
Y	-/-	2-46

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search

10 February 1995

Date of mailing of the international search report

17.02.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Hornig, H

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/10945

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/10945

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/10945

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